Lower Prevalence of BK Virus Infection in African American Renal Transplant Recipients: A Prospective Study

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Background. Because the occurrence of BK virus (BKV) nephritis is far less frequent than BK viremia or viruria, analysis of risk factors for BKV nephritis as an endpoint could lead to erroneous findings. We undertook a prospective study to evaluate the risk factors for the occurrence of BKV infections using BK viruria and viremia as endpoints.

Methods. Two hundred forty renal only transplant recipients were prospectively enrolled into our institutional review board-approved single center study to evaluate various aspects of posttransplant BKV infection. All patients were followed up for a minimum of 6 months posttransplant.

Results. Of the 240 subjects, 154 were whites, 61 African Americans, and 25 belonged to other races. A total of 94 developed BKV infection (any degree of BK viruria or viremia) whereas 146 developed no infection. Among these, 33 had BK viruria alone, 61 had BK viremia with viruria and 25 had significant viremia defined as BKV DNA more than 10,000 copies/mL of plasma. Lower proportion of African Americans developed BKV infection, 14 of 61 (23%), as opposed to whites, 67 of 154 (47%). Logistic regression model showed lower risk of any BKV infection in African American recipient race (OR, 0.38; 95% CI, 0.17–0.82; $P=0.016$) and higher risk of significant BKV infection with occurrence of acute rejection (OR, 3.9; 95% CI, 1.31–11.8; $P=0.015$). The Kaplan-Meier analysis shows a trend toward greater freedom from BKV infection in African Americans as opposed to other racial groups ($P=0.33$).

Conclusion. Renal transplant recipients of African American race had a lower risk of posttransplant BKV infection compared with whites, independent of other confounding risk factors.

Keywords: Kidney, Transplantation, Infection, BK virus.

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BK virus (BKV) infection is a common infection, unique to renal transplant recipients. This infection begins initially as asymptomatic BK viruria and subsequent viremia, ultimately progressing to BKV nephritis (BKVN). The prevalence of BKV infection in renal transplant recipients is estimated to be between 40% and 80% (*1*). In renal transplant recipients, approximately 35% to 47% of recipients will develop BK viruria within 3 months posttransplantation and 20% will develop BK viremia within 12 months posttransplant (*2–4*). The incidence of biopsy-proven BKVN can vary between 1% and 10%. Irreversible allograft failure is seen in approximately 30% of cases (range, 0–100) of BKVN (*5*). Graft survival rates after diagnosis of BKVN are much worse than other common conditions such as acute rejection and calcineurin inhibitor (CNI) toxicity (*6*).

Because of the substantial impact of BKV infection on renal allograft survival, several studies have tried to identify risk factors in an attempt to predict and prevent BKV infection. Most of these studies have been retrospective in nature, used center or national database, and focused on occurrence of BKVN as opposed to analyzing sensitive predisposing markers such as BK viremia or BK viruria. Because the occurrence of BKVN is far less frequent than BK viremia or viruria, analysis of risk factors for BKVN as an endpoint could lead to erroneous findings. In this prospective study, we evaluated the risk factors for the occurrence of BKV infections that included any BK viruria and BK viremia; and significant BKV infection as endpoints.

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RESULTS

Study Subjects

During the study enrollment period from July 2007 to July 2010, 318 de novo kidney transplants were performed at our center. Of these, 240 (76%) patients were enrolled and followed up until November 2010. Of these 240 patients, 94 developed BKV infection (any degree of BK viruria or viremia) whereas 146 developed no infection. Of the 94 patients with BKV infection, 33 had BK viruria alone and 61 had BK viremia with viruria. Of these, 25 had significant viremia. Renal biopsy was performed in 20 of them and 5 had histological features of BKVN without apparent renal dysfunction. Renal biopsy was performed for significant BK viremia in the absence of renal dysfunction. During the study duration, four recipients lost their grafts; two of them were African Americans and two were whites. In addition, 12 people died with a functioning graft during the study period. Of these, six were African Americans, five were whites, and one was Hispanic. None of the graft losses was secondary to BKV infection.

Demographics

Of the 240 recipients, 92 received kidneys from a living donor and the remaining 148 from a deceased donor. The mean donor age was 41.6 years (SD±13.2 years) and mean recipient age was 50.2 years (SD±11.7 years). Of the donors, 190 were whites, 29 were African Americans, and 21 belonged to other races. There were 122 (51%) male donors and 118 (49%) female donors. Of the recipients, 154 (64%) were whites, 61 (25%) were African Americans, and 25 belonged to other races (10%). The recipients were 142 (59%) men and 98 (41%) women. A total of 79 (32%) recipients had diabetes as the cause of end-stage renal disease. A total of 14 (15%) of 94 patients with BKV infection were African American and the rest 80 (85%) belonged to white and other races. Among the 25 patients with significant BK viremia, 4 were African Americans and 21 belonged to other races. The overall prevalence of BKV infection was lower among African Americans 14 of 61 (23%) as opposed to whites 67 of 154 (47%).

Immunological Variables

The mean class I and class II panel reactive antibody (PRA) were 15.4% (SD±29) and 10.5% (SD±25), respectively. A total of 23 (24%) patients in the BKV infection group and 29 (21%) patients without infection were sensitized (class I PRA >20%). Similarly, 12 (13%) patients in BKV infection group and 23 (17%) patients without any infection had class II PRA more than 20%. In the significant viremia group, 6 (24%) and 5 (20%) of 25 patients had class I and class II PRA more than 20%, respectively. The mean cold ischemia time (CIT) was 573 min (SD±517). The mean number of total human leukocyte antigen (HLA) match (A, B, DR) was 1.82 (SD±1.6) and mean number of total HLA mismatch (A, B, DR) was 4 (SD±1.6). A total of 126 (52%) recipients received Thymoglobulin as the induction therapy and 114 (48%) recipients received interleukin (IL)-2R blocker therapy. A total of 231 (96%) patients received Tacrolimus (Tac)/mycophenolate mofetil (MMF) combination therapy, 2 (1%) patients received Sirolimus/MMF, and 7 (3%) patients received Tac/Sirolimus combination immunosuppressive therapy. A total of five patients were switched from Tac/MMF to Sirolimus/MMF combination during the follow-up. None of patients in the study was on cyclosporine A-based regimen.

Doses of immunosuppressive medications were stratified per recipient race and posttransplant significant and insignificant BKV infection and at peak BK viremia. In subjects with significant BK viremia, at 1 month posttransplant, the mean dose of MMF and Tac was 1750 and 6 mg (mean Tac level, 7.1 ng/mL) in whites; 1800 and 10.8 mg (mean Tac level, 9 ng/mL) in African Americans; and 1714 and 7.4 mg (mean Tac level, 8.9 ng/mL) in other races, respectively. The corresponding doses for MMF and Tac in the insignificant BKV infection group was 1760 and 6.6 mg (mean Tac level, 9.2 ng/mL) in whites, 1928 and 11.8 mg (mean Tac level, 7 ng/mL) in African Americans, and 666 and 9.3 mg (mean Tac level, 6 ng/mL) in other races, respectively. On further analysis, at peak BK viremia for subjects with significant BKV infection the mean MMF and Tac dosage was 1437 and 5.4 mg (mean Tac level, 7.6 ng/mL) for whites, 1300 and 8.4 mg (mean Tac level, 8 ng/mL) for African Americans, and 1500 and 6 mg (mean Tac level, 7.7 ng/mL) for other races, respectively. In the insignificant BK Viremia group, the mean MMF and Tac dose was 1592 and 5.3 mg (mean Tac level, 7 ng/mL) for whites and 2000 and 8.8 mg (mean Tac level, 5.4 ng/mL), respectively, for African Americans. Thus, MMF dose at 1 month posttransplant and at peak BK viremia was not different per recipient race in both significant and insignificant BKV infection groups.

However, Tac doses were higher in African Americans with similar trough levels. A total of 193 (80%) patients had no acute rejection episodes, 45 (18.6%) had acute cellular rejection (ACR), and 4 (1.7%) had acute antibody mediated rejections. In the significant viremia group, 9 of 25 (36%) patients developed ACR and none developed acute humoral rejection. Of these, 4 were whites, 3 African Americans, and 2 from other races. Although in the insignificant infection group, 10 of 69 (14%) developed rejection. Among these, four were whites, three African Americans, and three from other race.

Univariate Analysis

The results of the univariate analysis are shown in Table 1. The analyses included two distinct entities:

a. Any BKV infection versus no infection: The recipient demographics, the donor demographics, the transplant variables, and posttransplant variables did not differ significantly between the BKV infection versus no infection recipients ($P>0.05$). However, recipient's African American race was associated with a lower risk of BKV infection as opposed to non-African Americans ($P=0.004$).
b. Significant BKV infection versus no infection: In this analysis, African American recipient race was associated with lower occurrence of significant BKV infection ($P=0.023$). Furthermore, other variables were not associated with occurrence of significant BKV infection.

Multivariate Analysis

To establish risk factors for various degrees of BKV infection, the occurrence of any BKV infection and significant BK viremia were analyzed as distinct entities.

TABLE 1. Baseline demographic factors, immunological variables, and posttransplant outcomes stratified by presence or absence of BKV infection and presence of significant BK infection

Risk factors	No BKV infection (N=146): Group I	BKV infection (N=94): Group II	*P* (I vs. II)	Significant BKV infection (N=25): Group III	*P* (I vs. III)
Donor variables					
Age (mean±SD) (yr)	41.5±13.6	41.8±12.7	0.86	41.7±11.3	0.98
Sex (M/F), n (%)	71/75 (48/52)	51/43 (54/46)	0.47	12/13 (48/52)	0.84
Race (W/B/O), n (%)	120/17/9 (81/11/8)	71/12/11 (74/13/12)	0.29	19/2/4 (76/8/16)	0.24
Type (LD/DD), n (%)	53/93 (36/64)	39/55 (41/59)	0.50	13/12 (52/48)	0.21
Age≥60 yr, n (%)	14 (10)	8 (9)	0.95		
Recipient variables					
Age (mean±SD) (yr)	50.5±11.3	49.5±123	0.53	52.1±13.5	0.51
Sex (M/F), n (%)	82/64 (56/44)	60/34 (64/36)	0.22	15/10 (60/40)	0.93
Race (W/B/O), n (%)	87/47/12 (60/34/6)	67/14/13 (71/15/14)	0.004	15/4/6 (60/16/24)	0.023
DM (Y/N), n (%)	50/96 (33/67)	29/64 (31/69)	0.76	8/17 (32/68)	0.95
Transplant variables					
Class I PRA>20%, n (%)	29 (21)	23 (24)	0.64	6 (24)	0.97
Class II PRA>20%, n (%)	23 (17)	12 (13)	0.52	5 (20)	0.90
HLA DR/AB/total mismatch	1.27/2.86/4.15	1.29/2.59/3.88	0.82, 0.09, 0.23	1.32/2.8/4.12	0.8/0.7/0.9
HLA DR/AB/total match	0.70/1.03/1.75	0.70/1.16/1.9	0.92/0.378/0.45	1.08/0.68/1.68	0.76/0.9/0.8
Total HLA match (>4), n (%)	9 (6.7)	8 (8.6)	0.67	1 (4)	0.96
Total HLA mismatch (>4), n (%)	76 (53)	40 (43)	0.17	14 (56)	0.97
Posttransplant					
Cold ischemia time (mean±SD) (min)	612±529	514±495	0.17	526±540	0.47
Induction therapy (thymo/IL-2), n (%)	60/79 (40/60)	44/50 (47/53)	0.52	12/12 (50/50)	0.80
Maintenance IS Tac/rapa+tac/rapa alone, n (%)	142/3/1 (97//2/1)	91/2/1 (97/3/1)	0.94	25/0/0 (100/0/0)	0.70
Rejection (none/ACR/AHR), n (%)	116/28/2 (79/19/2)	75/17/2 (80/18/2)	0.89	16/9/0 (64/36/0)	0.074

BKV, BK virus; W, whites; B, blacks; O, others; LD, living donor; DD, deceased donor; PRA, panel reactive antibody; HLA, human leukocyte antigen; IL-2, interleukin-2; thymo, thymoglobulin; IS, immunosuppression; Tac, tacrolimus; rapa, rapamycin; ACR, acute cellular rejection; AHR, acute humoral rejection.

a. The first model compared any degree of BKV infection with those without infection. This analysis showed African American recipient race to be independently protective against development of BKV infection (OR, 0.38; 95% CI, 0.17–0.82; $P=0.016$) (Fig. 1). None of the other variables were found to be significantly associated with development of BKV infection.
b. The second model compared significant BKV infection with those without any infection. It revealed the occurrence of posttransplant acute rejection episodes as a significant risk factor for significant BKV infection (OR, 3.9; 95% CI, 1.31–11.8; $P=0.015$). In this model, all other variables including recipient race were not significant.

To further explore the role of recipient race in BKV infection, we constructed Kaplan-Meier survival curves to study freedom from BKV infection over the duration of study stratified by the recipient race (Fig. 2). The analysis was censored for graft loss from any cause including death. The KM analysis shows a trend towards greater freedom from BKV infection in African Americans as compared with whites and other races ($P=0.33$). The incidence of infection was lowest in African Americans, followed by whites and then other races.

DISCUSSION

Our study is the largest single center prospective study to date to evaluate the risk factors for BKV infection using BK viruria and viremia as endpoints. We evaluated several traditional risk factors for BKV infection identified in previous studies. These included recipient age, deceased donor status, male gender, HLA mismatch, thymoglobulin use, Tac-MMF combination use, occurrence of acute rejection, and placement of ureteral stents as risk factors for BKV infection (*2*, *7–11*). A recent review of literature from our group summarized these risk factor studies and highlighted the low positive and negative predictive values of these reported risk factors for BKV infection (*12*). In our study, however, none of these risk factors were found to be significantly associated with the BKV infection. On the other hand, we found recipients with African American race to be protective against development of BKV infection both in univariate and multivariate analysis. This effect persisted even after controlling for other factors traditionally associated with BKV infection. The recipient race has not been previously reported as a risk factor or a protective factor for BKV infection in any prospective studies. It is likely that recipient race is a surrogate marker for some factor which we have not yet identified and controlled in the

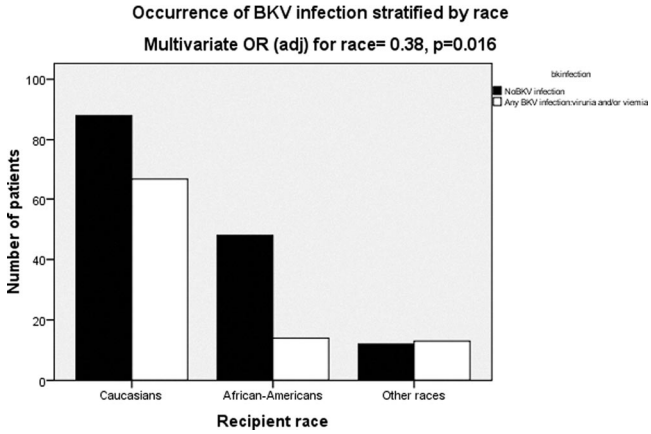

FIGURE 1. Protective effect of African American race on development of BK virus (BKV) infection.

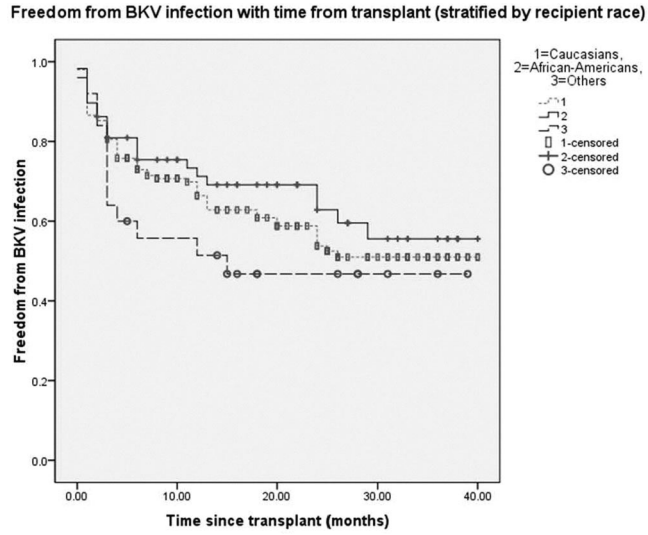

FIGURE 2. Freedom from BK virus (BKV) infection with time from transplant, stratified by recipient race.

multivariate analysis. Furthermore, it is plausible that certain HLA phenotypes in African Americans may be protective to BKV infection. As an example, a higher incidence of sustained BK viremia in donor and recipient pairs with absent HLA-C7 allele has been reported in the literature (*13*). The recipient race was a significant factor for the occurrence of clinically significant BKV infection only in univariate analysis (Table 1). We believe it is likely due to fewer patients (n=25, 10%) in this group (Table 2). The occurrence of any BKV infection is an important early marker for the progression toward significant infection leading to BKVN. Thus, the observation from our study of lower odds of BKV infection in African American population is an important finding.

Additional analysis was performed to explore the differential impact of recipient race on early graft loss including death and its relationship to the occurrence of BKV infection. Notably, of the 18 patients who were censored for graft loss, 10 had already developed BKV infection before graft loss or death with a functioning graft. Of the remaining eight patients, only three were African American and the rest were whites.

Awadalla et al. (*9*) in their study on 40 patients with BKV nephropathy proposed that HLA mismatching promoted the development of BKV nephropathy through rejection-related inflammatory processes with background heavy immunosuppression causing virus reactivation and tubular injury. From our large prospective study, we did not find any correlation between degree of HLA mismatches and BKV infection in both univariate and multivariate analyses.

Our study did find occurrence of acute rejection as an independent risk factor for development of significant BKV infection. This is perhaps due to aggressive approach toward transplant renal biopsy in patients with significant BK viremia both before and after the reduction in immunosuppression. Such an approach was not practiced in patients without BKV infection. Nevertheless, it is intuitive to consider that occurrence of acute rejection, the treatment of acute rejection with additional immunosuppressive medications and occurrence of acute rejection postreduction in immunosuppression for BKV infection may be playing a role in identifying this as a risk variable.

At our center, majority (98%) of our patients is on Tac-MMF combination and hence it was not possible to evaluate the protective role of cyclosporine-based immunosuppression in BKV infection (*3*, *10*). More likely, it is the overall immunosuppression and not just one agent that leads to BKV infection. This infection has also been reported with newer CNI-free regimens that include Belatacept (*14*). Further strengthening this contention is higher incidence of BKV infection in CNI-free immunosuppression based on JAK 3 inhibitor (*15*). Also, previous studies have identified conflicting reports on presence of ureteral stents as contributing to BKV infection (*16*, *17*). At our center, all transplant patients undergo ureteral stent placement at the time of surgery. Hence, this factor could not be evaluated as a risk factor.

The strengths of our study are a prospective study and single-center experience. In addition, all BKV DNA was performed locally by the same laboratory, and thus avoiding interlaboratory variability. Our group also had an excellent compliance with approximately 100% follow-up. Our study is unique by its prospective nature, clearly defined types of BKV infection before the initiation of the study; with a uniform approach towards immunosuppressive management, treatment of acute rejection, and treatment of significant BKV infection. Possible limitations of our study include relatively smaller numbers of patients in significant BKV infection and BKVN groups. The Kaplan-Meier curves show a trend towards lower incidence of BKV infection in African Americans. However, this has to be validated from a larger cohort. A larger study population could have identified the same risk variables for subjects developing significant BKV infection and BKVN. Perhaps, a separate study could be conducted to evaluate the differential risk factors for early and late onset BKV infections. Additionally, humoral and ACRs could be studied as separate risk factors for BKV infection. In our study, few patients had acute antibody mediated rejection and they were equally distributed among the BKV-infected and noninfected groups. Further study could also be conducted to analyze the role of specific donor-recipient HLA mis-

TABLE 2. Summary of two logistic regression models and highlighting recipient race and occurrence of acute rejections as risk factors for BKV infection and significant BKV infection, respectively

Risk factor assessed	Model 1 (any BKVI vs. none) (N=94 vs. 146) Adjusted OR/95% CI	Model 2 (significant BKVI vs. none) (N=25 vs. 146) Adjusted OR/95% CI
Donor source: LD vs. DD	0.97 (0.47–2.1)	2.5 (0.67–9.27)
Donor age (≥60 vs. <60) (yr)	1.12 (0.42–3.1)	0.38 (0.04–3.5)
Donor race (AA vs. others)	1.24 (0.49–3.2)	0.71 (0.14–3.59)
Recipient race (AA vs. others)	0.38/(0.17–0.82, P=0.016)	0.70 (0.19–2.53)
Recipient age (≥60 vs. <60) (yr)	0.93/(0.47–1.86)	2.48 (0.85–7.2)
Induction therapy (thymo vs. IL-2)	0.76 (0.38–1.54)	0.61 (0.19–1.84)
PRA I/II (>20 vs. ≤20) (%)	0.96 (0.44–2.1)	1.23 (0.3–4.3)
CIT (>840 vs. ≤840) (min)	0.85 (0.92–1.71)	2.70 (0.73–9.9)
HLA mismatch (>4 vs. ≤4)	0.67 (0.38–1.21)	1.70 (0.62–4.6)
Rejection (all rejection vs. none)	0.83 (0.41–1.71)	3.9 (1.31–11.8, P=0.015)

BKVI, BK virus infection; LD, living donor; DD, deceased donor; AA, African American; PRA, panel reactive antibody; CIT, cold ischemia time; HLA, human leukocyte antigen.

matches or HLA epitopes in the development of BKV infection. This study is limited due to standard analysis using HLA-A, -B, and DR matches and did not include HLA-C locus and other genotypes for correlation to BKV infection.

Conclusion

Renal transplant recipients of African American race had a lower risk of posttransplant BKV infection compared with whites and this effect was independent of other potentially confounding risk factors.

MATERIALS AND METHODS

Study Subjects

A total of 240 renal only transplant recipients were prospectively enrolled into our institutional review board-approved study before or immediately (within 5 days) after transplantation from July 2007 to July 2010. These patients were followed up for a minimum period of 6 months posttransplant.

Immunosuppression

Immunosuppression consisted of induction with Thymoglobulin (total 3–6 mg/kg) or two doses of IL-2R blocker (Basiliximab) based on our center's immunological risk stratification. In general, thymoglobulin was administered as induction agent for younger African American recipients, elevated PRA and repeat transplants or any degree of positive cross match. The maintenance therapy consisted of MMF, Tac, and prednisone. ACR diagnosed with biopsy was treated with IV solumedrol (3–5 mg/kg daily for 3–5 days) for Banff stage I and thymoglobulin 1.5 mg/kg/daily for 3 to 7 days for steroid-resistant acute rejection and Banff stages II and III.

Data Collection and BKV DNA Testing

Baseline information on donors, recipient, transplant, and posttransplant variables was collected (Table 1). Quantitative plasma BKV DNA at baseline and plasma and urine BKV DNA at 1, 3, 6, 12, and 24 months after transplantation were tested. Additional plasma BKV DNA estimations were performed, per physician discretion, after detection of BK viremia or for patients with renal dysfunction.

BKV DNA Testing Methods

Monitoring of viral load by real-time polymerase chain reaction was performed using combined VP2 and VP3 segments of BKV as targets. Primer and sequence-specific hybridization probe were used in the amplification reaction. Primers used were synthesized according to Hoffman et al. (*18*). The BKV-specific probe, Penny3, was designed using Primer Express software in our laboratory. On completion of the polymerase chain reaction reaction, a standard curve was plotted and patient sample values calculated and BKV copy numbers per milliliter of patient plasma or urine were reported.

Follow-Up

All patients were followed up at our center. Renal biopsy was performed when patients had a change in serum creatinine more than or equal to 0.3 mg/dL or a decrease in estimated glomerular filtration rate less than or equal to 10% to 15% from baseline or with significant BKV infection.

Severity of BKV Infection

BKV infection was stratified as significant (defined as plasma BKV DNA≥10,000 copies/mL) (*19*) or insignificant BKV infection (defined as BKV DNA<10,000 copies/mL of plasma or BK viruria alone).

Treatment of BKV Infection and Follow-Up

Patients with significant infection alone were treated with reduction in immunosuppression without any antiviral therapy. Details about therapy for BKV infection have been published before (*20*). Repeat renal biopsy was performed when patients developed renal dysfunction after reduction in immunosuppressive therapy.

Outcome Measures and Variables

The following two outcome measures (endpoints) were assessed: (A) BKV infection, defined as any degree of BK viruria alone or any degree of BK viremia and (B) significant BKV infection. Univariate analysis was performed with each of the outcome variables.

The variables included donor source (living vs. deceased), donor and recipient demographics (age, gender, and race), recipient diabetes mellitus, type of induction therapy (thymoglobulin vs. IL-2R blockers), maintenance immunosuppression, class I and II PRA %, CIT, degree of AB/DR/total HLA match and mismatch, and occurrence of biopsy-proven acute rejection.

Two separate logistic regression models were then constructed with same endpoints as for univariate analysis. For these analyses, only 9 of 16 total variables were included in the final models based on the results of the previous univariate analyses. These variables included donor source and age, recipient age and race, type of induction therapy, HLA mismatch, PRA class I and II % (combined into a single category of PRA >/<20%), CIT and occurrence of acute rejection. Because nearly all of our transplant recipients were on MMF- and Tac-based immunosuppressive regimen, the maintenance immunosuppression type was not included in the final models.

Statistical Analysis

SPSS software version 16 was used for statistical analysis. Categorical and continuous variables were analyzed using χ^2 test and Student's *t* test, respectively. A *P* value less than 0.05 was considered statistically significant.

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